

## REMARKS

Claims 1, 102, 105 and 106 are under consideration. Claim 1 has been canceled without prejudice to the subject matter therein. Claims 102 and 105 have been amended. Support for the amendments may be found throughout the specification, for example, at Figure 4, [0135] to [0138], and [0140] to [0141] of corresponding Publication No. 2004/0127416.

### ***Rejection under 35 U.S.C. § 103***

On page 2 of the Final Office Action mailed December 4, 2009, the Examiner maintains the rejection of claims 102, and 105-106 under 35 U.S.C. § 103(a) “as being unpatentable over Rieu et al (Journal Cell Biology 1994 v127 pages 2081-2091 ...) and Laplantine et al (Journal of Cell Science 2000 v113 1167-1176)...” Applicants traverse the rejection.

The claimed invention provides for a therapeutic bioconjugate consisting of a hydrophilic polymer; and a peptide comprising SEQ ID NO:124, wherein the peptide of the therapeutic bioconjugate binds to a cell expressing ICAM and the hydrophilic polymer inhibits monocyte adhesion to the cell.

Rieu refers to the binding site for neutrophil adhesion inhibitor (NIF) in  $\beta 2$  integrin complement receptor type 3 (CD11b/CD18). ICAM binding is not discussed in Rieu. The Examiner asserts, on page 4 of the Action, that “Rieu teach that the A-domain may be useful for treating hookworm infection ... notes that certain peptides did not absorb adequately ... Thus one would be motivated to **further study** the A-domain NIF interaction.” (Emphasis added). The Examiner’s assertion is no more than an invitation to try, related to A-domain NIF interactions and not to ICAM binding.

In that regard:

what would have been “obvious to try” would have been to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many choices were likely to be successful. ... In others what was “obvious to try” was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only **general guidance** as to the particular form of the claimed invention or how to achieve it. *In re O’Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988) (emphasis added).

The Examiner does not explain, for example, where Rieu provides a reasonable expectation of success regarding ICAM binding with the claimed peptide. More specifically, Rieu refers to the characterization of neutrophil adhesion inhibitor, NIF, a protein that inhibits neutrophil spreading and adhesion to endothelial cell monolayers by binding to CR3, a member of the  $\beta 2$  integrin subfamily expressed on activated neutrophils. Rieu states that “the binding cite for *NIF* in the CD11bA-domain is broad, comprised of primarily *two* centrally located *overlapping* peptides *A6 and A7*, with *additional contribution by two peptides* located at the beginning (A1) and end (A12) of the domain.” (Emphasis added.)

Hence, despite the presence of the claimed amino acids in A7, Rieu actually *teaches away* from the specific 15-mer of the claims by teaching a binding cite having a “**broad interactive region**” combining overlapping peptides of which A7 is only a part. Moreover, Rieu used peptides that were bound to a solid surface (page 2082, col. 2, page 2083, col. 1), and “blocking” activity assays compared antibodies or NIF proteins, and did not access directly the ability of any particular peptide to prevent association of NIF to neutrophils. Indeed, despite the Examiner’s inference that the peptide of A7 would have the claimed bioactivity, it does *not* have the bioactivity of the claimed bioconjugate:

Unconjugated peptides, dextran, and the inactive peptide conjugate inhibited cell adhesion poorly, suggesting that *only the combined effect of specific binding of active peptide conjugates to ICAM and formation of an ICAM-bound nonadhesive dextran layer promoted reduced monocyte adhesion* to TNF- $\alpha$  stimulated, ICAM-expressing BECs. (at [0138], emphasis added).

Thus, Rieu and Laplantine do not suggest the claimed therapeutic consisting of the claimed peptide conjugated to a hydrophilic polymer, in which the peptide of the bioconjugate binds to a cell expressing ICAM and the hydrophilic polymer inhibits monocyte adhesion to that cell.

More specifically, Laplantine refers to the intracellular domain of the  $\beta 1$  subunit that was generated to contain an additional N-terminal cysteine and immobilized on a carboxymethyl dextran sensorchip using thiol coupling. The claimed invention does not relate to sensor chips, and there is nothing in Laplantine to suggest the use of thiol coupling for any other purpose than the production of sensor chips. The Examiner states that “[Because] Laplantine teach surface Plasmon resonance as a specific method to investigate integrin interactions one would be motivated to use the method of

Laplantine.” But the claimed invention has nothing to do with Plasmon resonance, and the Applicants do not even discuss Plasmon resonance in the instant specification. Laplantine is hardly an invitation to try, much less support for an obviousness rejection.

The combination of Rieu and Laplantine does not support the obviousness rejection because the mere binding of a peptide to dextran does not teach the claimed *therapeutic* conjugate. There would be no reason to combine the biosensor technology of Laplantine with the assays of Rieu, neither of which suggest the claimed bioconjugate consisting of a peptide and hydrophilic polymer in which the peptide of the therapeutic bioconjugate binds to a cell expressing ICAM and the hydrophilic polymer inhibits monocyte adhesion to that cell. For example, Rieu refers to binding of  $\alpha$  subunits (CD11a, CD11b, and CD11c) and states that  $\beta 2$  (CD18) subunit does not bind NIF (see, e.g., Laplantine’s Figure 3 and legend on page 2086), while Laplantine refers to  $\beta 1$  subunit and its interaction with  $\alpha 3$  in the context of laminin binding. Rieu and Laplantine, in combination, do not suggest the interaction of the claimed bioconjugate with ICAM-expressing cells. Additionally, the dextran-bound compositions of Laplantine included a sensor chip that is not included in the claimed invention consisting of a peptide and a hydrophilic polymer.

The Examiner, on page 5, states that “both Rieu and Laplantine are drawn to methods of identifying interacting regions between integrins and interaction partners. These methods, however, constitute an invitation to try general procedures or numerous possibilities, with no direction to the claimed therapeutic bioconjugate. For example, the Examiner acknowledges that “Rieu teach a method in which peptides were *adsorbed* to plastic wells,” and “Laplantine teach a method in which selected peptides … were *immobilized* on dextran,” which do not provide for the claimed invention consisting a particular peptide that binds to ICAM-expressing cells conjugated to dextran, where the dextran is not associated with immobilization, but blocks adhesion of leukocytes to ICAM-expressing cells. Simply put, when dextran is attached to a sensor chip there is no suggestion that it will inhibit adhesion between a leukocyte and a cell that expresses ICAM.

Moreover, although the Examiner notes, on page 7 of the Action, that “Rieu teach that the A-domain may be useful for treating hookworm infections,” this does not suggest that the claimed peptide, when conjugated to dextran, inhibits adhesion between a leukocyte and a cell that expresses *ICAM*. Regardless of Rieu “recognize[ing] the goal of mapping of the binding site,” (Action at page 8), this is the NIF binding site, not the ICAM binding site, and Rieu and Laplantine do not combine to teach the specific ICAM binding of the claimed peptide, or that the claimed

peptide, when conjugated to dextran, inhibits adhesion between a leukocyte and a cell expressing ICAM.

The Court has instructed that “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741 (2007). Regarding the pending claims, the combination of Rieu and Laplantine do not even provide for each of the limitations of the pending claims: a therapeutic bioconjugate consisting of a peptide, CNAFKILVVITDGEK, conjugated to a hydrophilic polymer, wherein the peptide binds to cells that express ICAM, and the polymer inhibits the binding of leukocytes to those ICAM-expressing cells.

On page 10 of the Action, the Examiner asserts that the combination of Rieu and Laplantine arrive at “the problem to be solved,” citing *In re Keller*. But Rieu addresses NIF binding to the  $\alpha$  subunits of  $\beta 2$  integrins; and Laplantine addresses  $\beta 1$  binding to its counterpart  $\alpha$  subunits. The problem solved by the claimed conjugate relates for example, to inhibiting ICAM-associated cell adhesion. Neither Rieu nor Laplantine address ICAM-expressing cells, nor propose any means of blocking leukocyte adhesion to ICAM-expressing cells. Hence, Applicants urge that the combination of Rieu and Palantine do not support a § 103 rejection, and request that this rejection be withdrawn.

## CONCLUSION

For at least the reasons set forth above, Applicants respectfully submit that this application is in condition for allowance. Favorable consideration and prompt allowance of the claims are earnestly requested. The Commissioner is hereby authorized to charge any payment deficiency to Deposit Account No. 19-2380 referring to Attorney Docket No. 049954-004100.

Should the Examiner have any questions that would facilitate further prosecution or allowance of this application, the Examiner is invited to contact the Applicants’ representative designated below.

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By: /Mary S. Webster, Reg. No. 37,156 /  
Mary S. Webster

**Customer No. 22204**  
NIXON PEABODY LLP  
Suite 900  
401 9th Street, N.W.  
Washington, DC 20004-2128  
Telephone: (202) 585-8000